



Armed Forces College of Medicine AFCM



Biochemical Basis of Pulmonary Diseases

By

Fayda Elazazy

**Professor & head of Medical
Biochemistry and
Molecular Biology
Department**



By the end of this lecture the student will be able to:

- 1. Explain the biochemical basis of cystic fibrosis, α 1 antitrypsin deficiency and respiratory distress syndrome.**
- 2. Describe the structure of elastin and pulmonary surfactant.**
- 3. Correlate the signs and symptoms to the biochemical basis of cystic fibrosis, α 1**

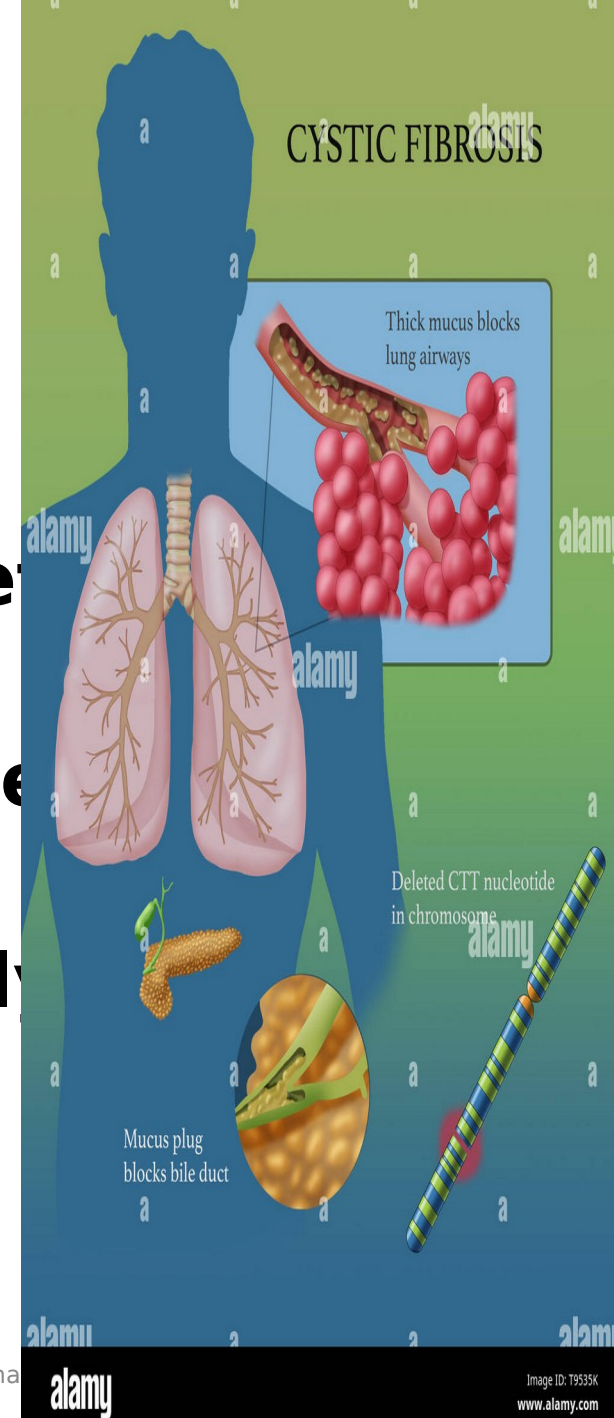




What is cystic fibrosis (CF)?

An **autosomal recessive** gene characterized by

1. Chronic respiratory disease
2. Pancreatic insufficiency
3. Elevation of sweat electrolyte
4. Male infertility

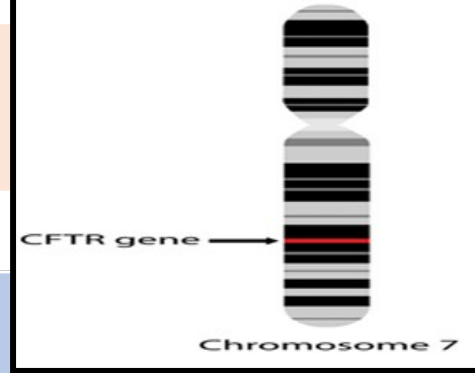


Causes of CF?

Mutation in the gene that encodes a membrane protein called **C**ystic **F**ibrosis **T**ransmembrane **C**onductance **R**egulator **CFTR**.

This affects the movement of salt and water in and out of cells result in formation of **thick, sticky mucus** in the body's tubes particularly the **lungs and digestive** system with **recurrent infections**.

Genetics of CF

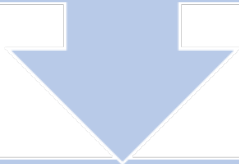


The most common mutation is

3 base pair deletion leading to absence of phenylalanine at position 508 (delta F 508) of the CFTR protein

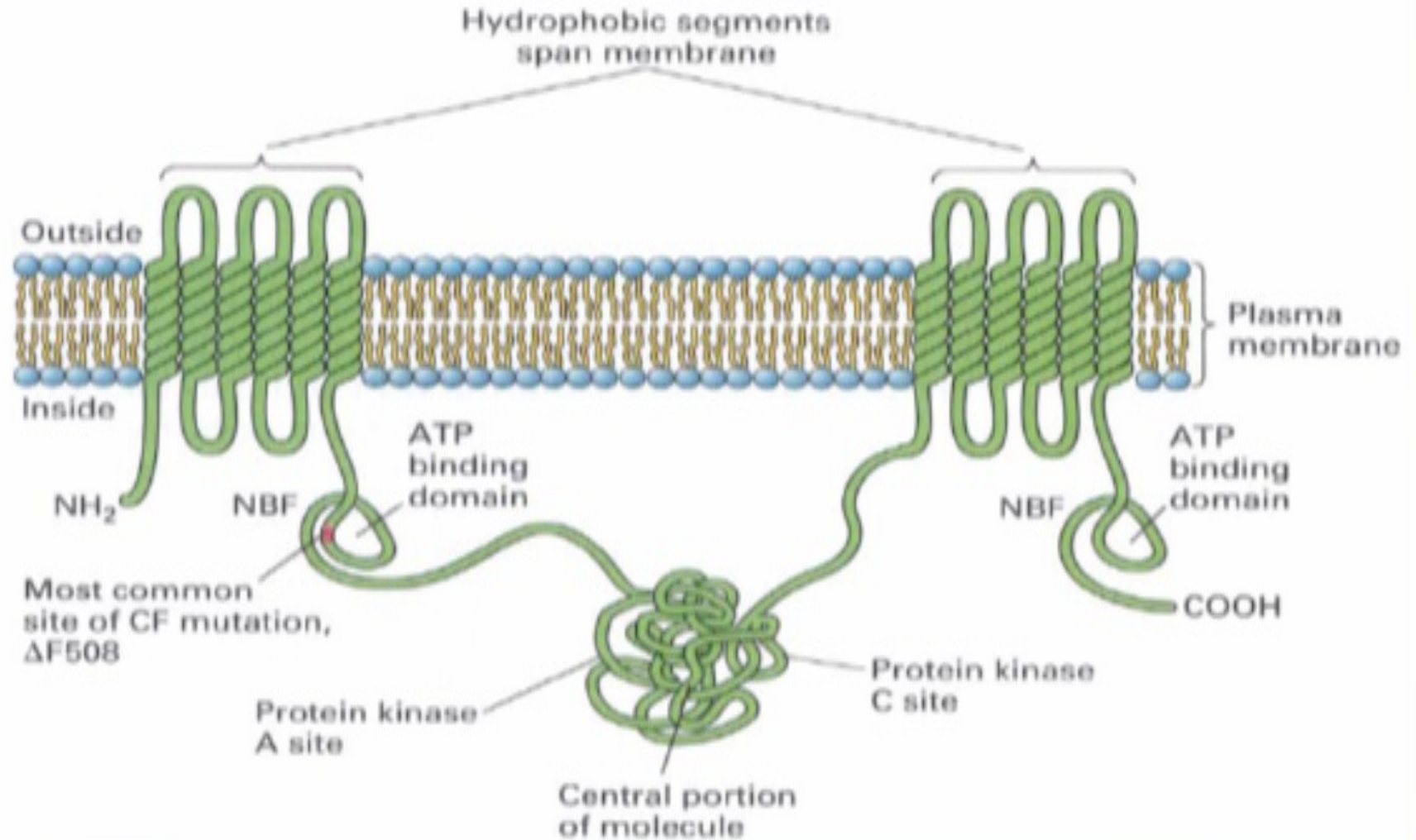


The mutant protein is not correctly mature and can not reaching the plasma membrane



delta F 508 mutation leads to improper processing and intracellular degradation of the CFTR protein

CFTR



The CFTR protein

- ❖ Single polypeptide chain
- ❖ Found in the plasma membrane of normal epithelial cells forming a channel.
- ❖ **It is cAMP regulated chloride channel**
- ❖ The channel is normally closed but opens
- ❖ When phosphorylated by protein kinase A. So regulate chloride and fluid secretion
- ❖ When the protein is not working correctly, chloride becomes trapped inside cells.
- ❖ Also regulates other ion channels like sodium (Na^+)

Functions of CFTR protein

CFTR is a channel required for proper salt-water transport across epithelium, including the lung and the gut

- 1) Volume absorbing (airway, distal intestine)
- 2) Salt absorbing (sweat ducts)
- 3) Volume secretory (proximal intestine, pancreas)

Therefore, **dysfunction in CFTR gene** leads to different effects on patterns of electrolyte and water transport.

* **CFTR overactivation** due to bacterial toxins causes severe diarrhea (e.g., in cholera)

* **Impaired activation** due to mutations underlies cystic fibrosis, a lethal disease

Pathophysiology



Lung

High rate of sodium absorption and **low rate of chloride secretion**

reduces salt and water content in mucus

Mucus adheres to airway surface **thick sticky mucus**, leads to decreased mucus clearing and predisposition to infections

Pancreas:

Absence of CFTR decreases secretion of bicarbonate

Leads to retention of enzymes in the pancreas, destruction of pancreatic tissue.

Intestine

Decrease in water secretion leads to thickened mucus **thick sticky mucus** and obstruction of small and large intestine

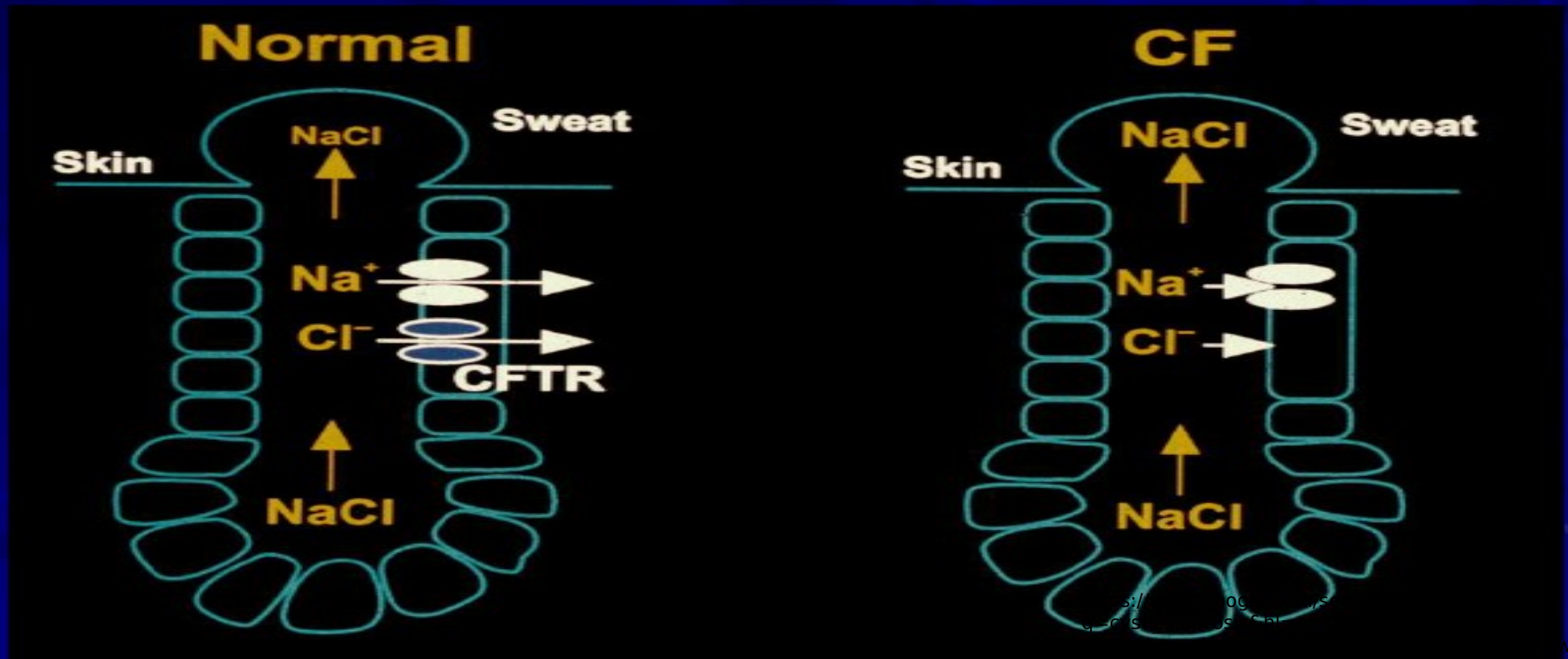
Pathophysiology



Sweat:

Normal volume of sweat

Inability to reabsorb NaCl from sweat as it passes through sweat duct



Clinical Picture of Cystic Fibrosis

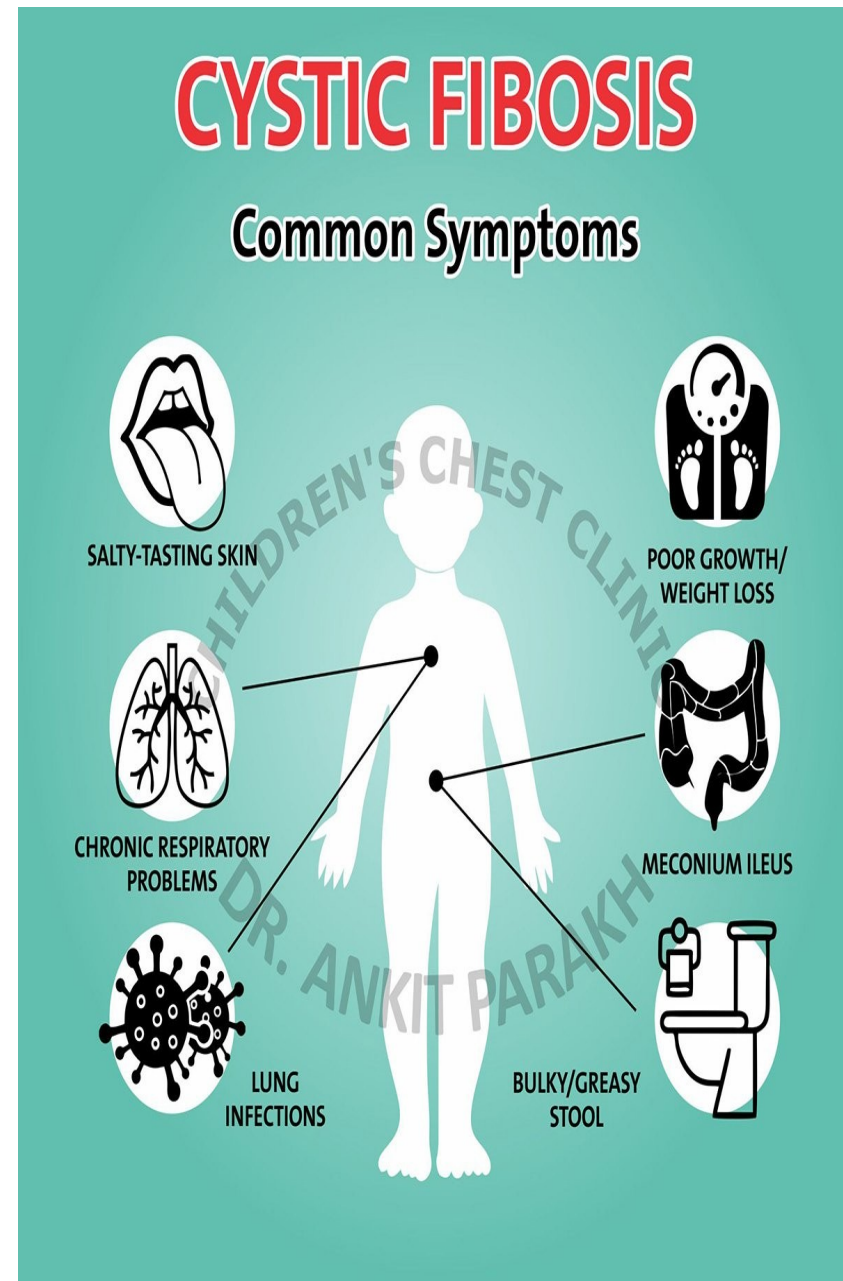
**Impaired lung
clearance of mucous**

**Recurrent lung
infection and
inflammation**

Pancreatic damage

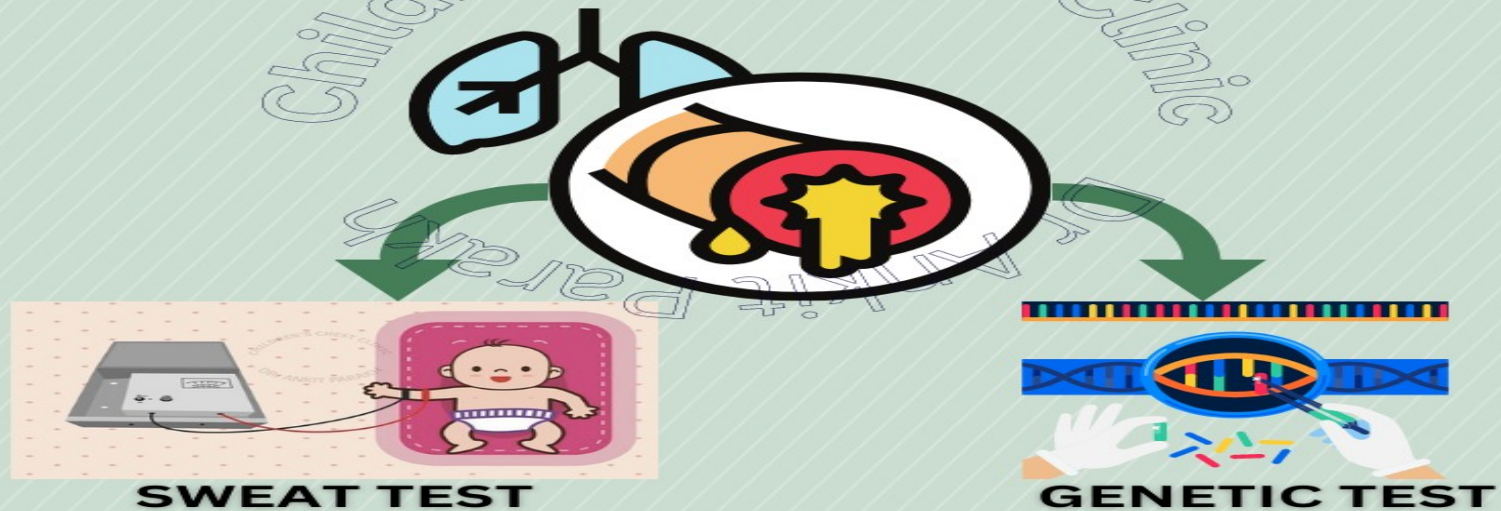
Impaired digestion

Infertility



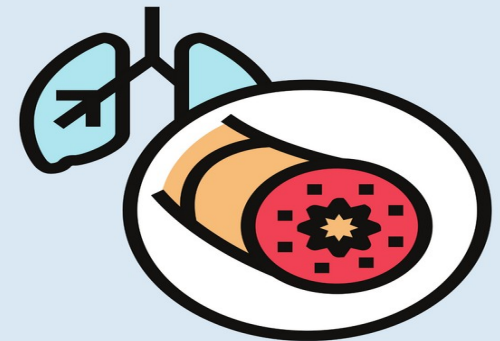
Cystic Fibrosis

DIAGNOSIS



Diagnosis of Cystic Fibrosis

- Blood test.
- Sweat test: To measure the salt present in a person's sweat, as high levels of salt can help in detecting CF.
- DNA test: To check for mutations to the gene.
- Chest X-rays.
- Tests to check lung function.



Treatment

Major objectives

- 1. Promote clearance of secretions**
- 2. Control lung infection**
- 3. Provide adequate nutrition**
- 4. Prevent intestinal obstruction**
- 5. Gene therapy**

Answer the following question

Cystic fibrosis is caused by which of the following?

- A. A defective gene that leads to the making of an abnormal protein
- B. Someone who eats too much salt
- C. A defective gene that causes abnormalities in the brain
- D. The cause is not known

Elastin

Elastin fibers are found in:

- **Lungs**
- **Walls of large arteries**
- **Elastic ligaments**

Elastin provides elasticity

Elastin fibers are highly branched that can be stretched to several times their normal length and recoil to their original shape when stretching force is released

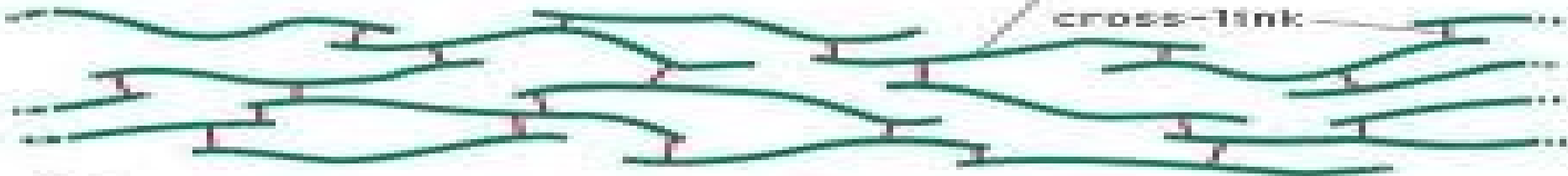


STRETCH

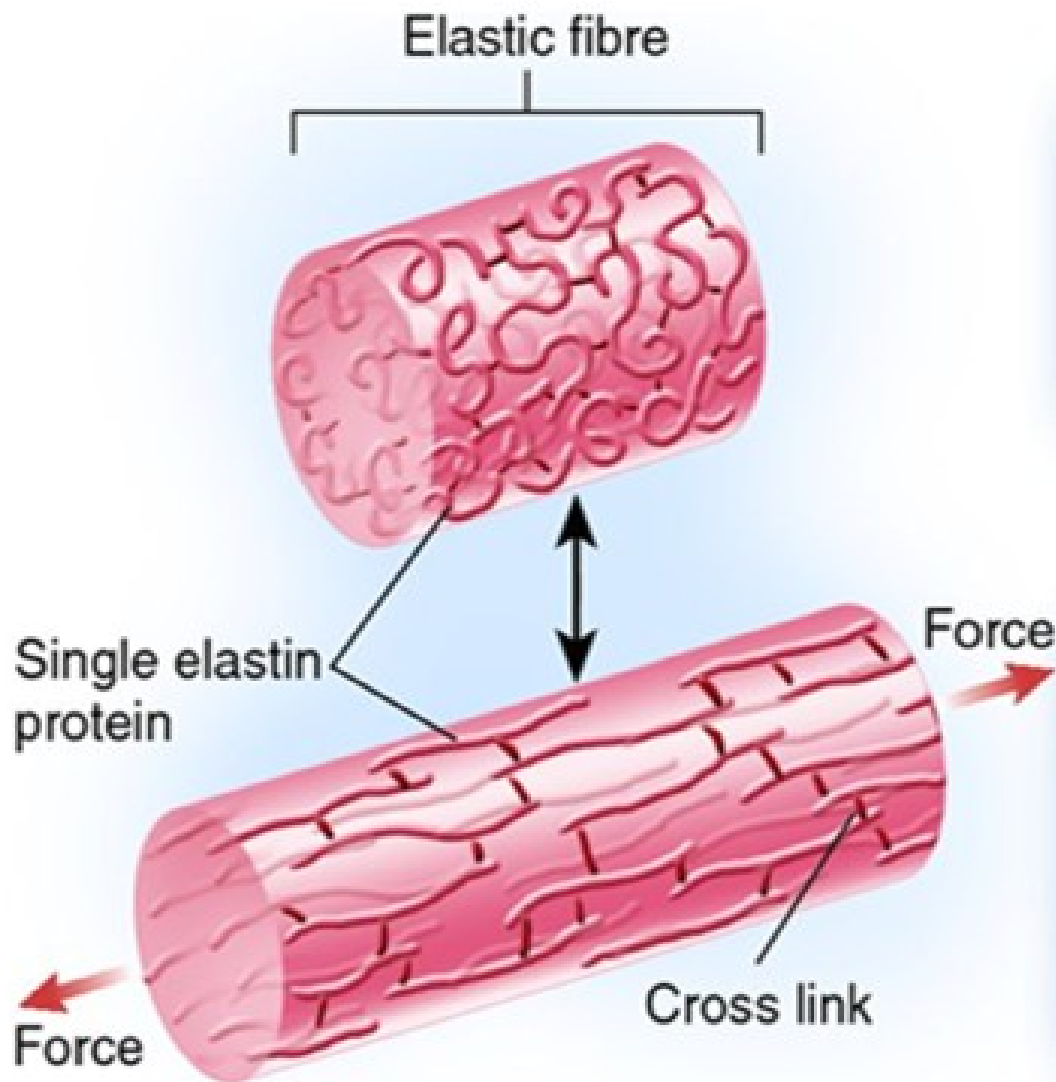
RELAX

single elastin molecule

cross-link



(B)



In the absence of a stretching force, the elastin proteins are in a compact conformation.

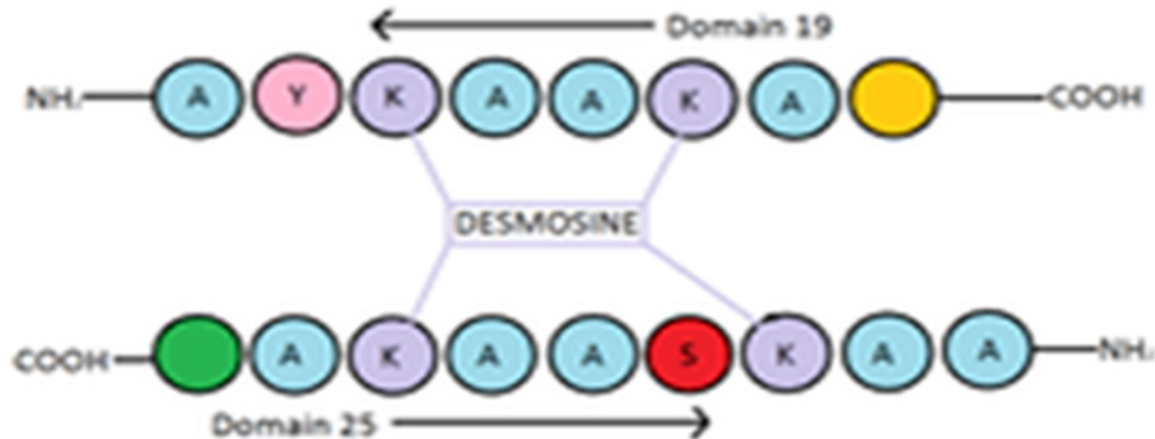
When subjected to a stretching force, the elastin proteins elongate but remain attached to each other via cross links.

Structure of elastin

- The basic unit (precursor) of elastin fibers is tropoelastin
- Tropoelastin is linear polypeptide composed of about 700 AAs that are nonpolar(e.g **glycine**, **valine** and **alanine**)
- Elastin is **rich in lysine** and **proline**, **little hydroxyproline** and **hydroxylysine**

Structure of elastin

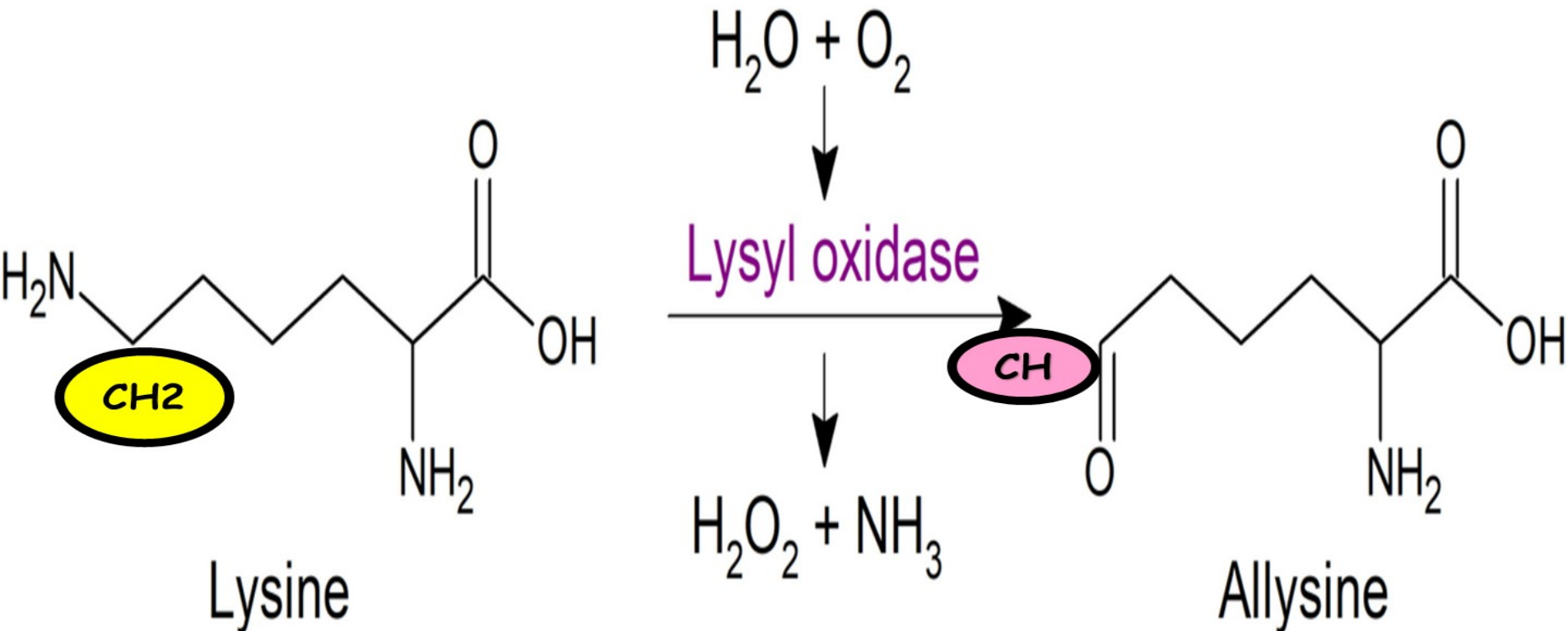
- In the extracellular space, **tropoelastin** interacts with fibrillin
- **Covalent cross links** connect elastin polypeptide chains into a network
- The **cross links** may occur **within the same polypeptide chain (intrachain)** or involve **2 to 4 different polypeptide chains (interchain)**
- The cross links involve **desmosine**



Desmosine

- It is a heterocyclic structure formed of 3 Allysine residues with one lysine.

N.B. Allysine residues are formed through oxidative deamination of lysyl side chains of tropoelastin by lysyl oxidase enzyme



α 1 antitrypsin (AAT)

Most AAT found in plasma is synthesized and secreted by the liver

Extrahepatic synthesis occurs in monocytes and alveolar macrophages (important in the prevention of local tissue injury by elastase)

Is also present in blood and other body fluids

Role of α 1 antitrypsin in the lungs

It inhibits **Elastase enzyme** (proteolytic enzyme) which is secreted by neutrophils and degrades **Elastin** & other structural proteins of alveolar walls.

Causes of α 1 antitrypsin deficiency

Results from different mutations of AAT gene causing deficiency of the protein

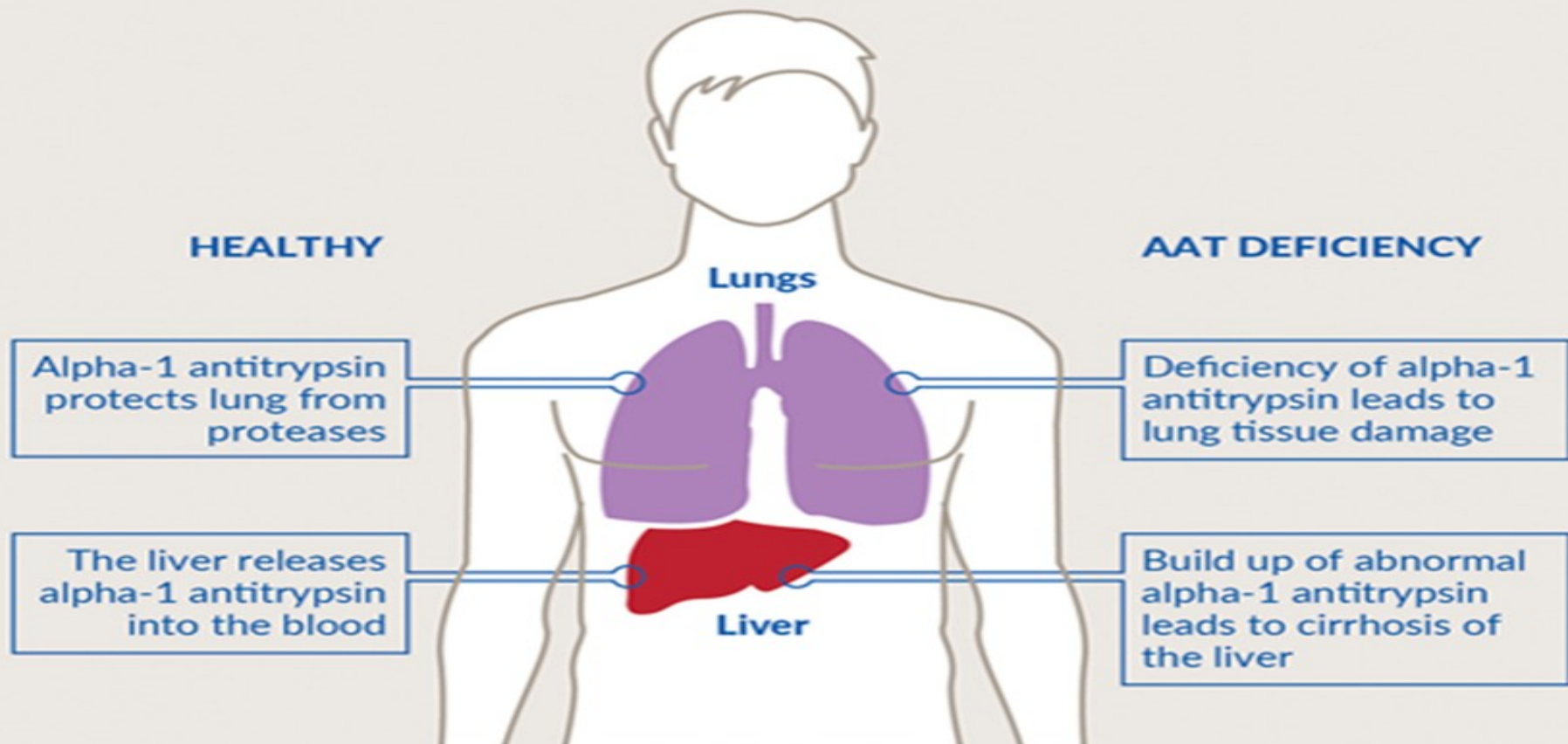
The most clinically widespread is one single purine base mutation (GAG to AAG, resulting in the substitution of lysine for glutamic acid at position 342 of the protein)

The mutation causes the normally monomeric AAT to polymerize within the endoplasmic reticulum of hepatocytes, resulting in decreased secretion of AAT by the liver

Causes of $\alpha 1$ antitrypsin deficiency

The **polymer that accumulates in the liver** results in cirrhosis and the blood levels of AAT are reduced, decreasing the amount that gets to the alveoli

This causes **loss of elastase enzyme inhibition** resulting in degradation of elastin of alveolar walls inducing a disease called emphysema



Smoking and Emphysema

Methionine 358 in AAT is required for the binding of the inhibitor to its target proteases.

Smoking causes the **oxidation** and subsequent **inactivation** of the **methionine**, thereby rendering the inhibitor powerless to neutralize elastase.

Smokers with AAT deficiency, therefore, have a considerably elevated rate of lung destruction and a poorer survival rate than nonsmokers with the deficiency.

Emphysema: A type of Chronic Obstructive Pulmonary Diseases (COPD) with damage to the lung alveoli

SMOKING DAMAGES YOUR LUNGS

Chronic obstructive pulmonary disease (COPD)

Chronic bronchitis

Emphysema

Pneumonia

Asthma

Tuberculosis



COPD CAUSES:

- ✓ Smoking
- ✓ Air pollutants / other irritants
- ✓ Genetic /epigenetic factors

SYMPTOMS OF COPD:

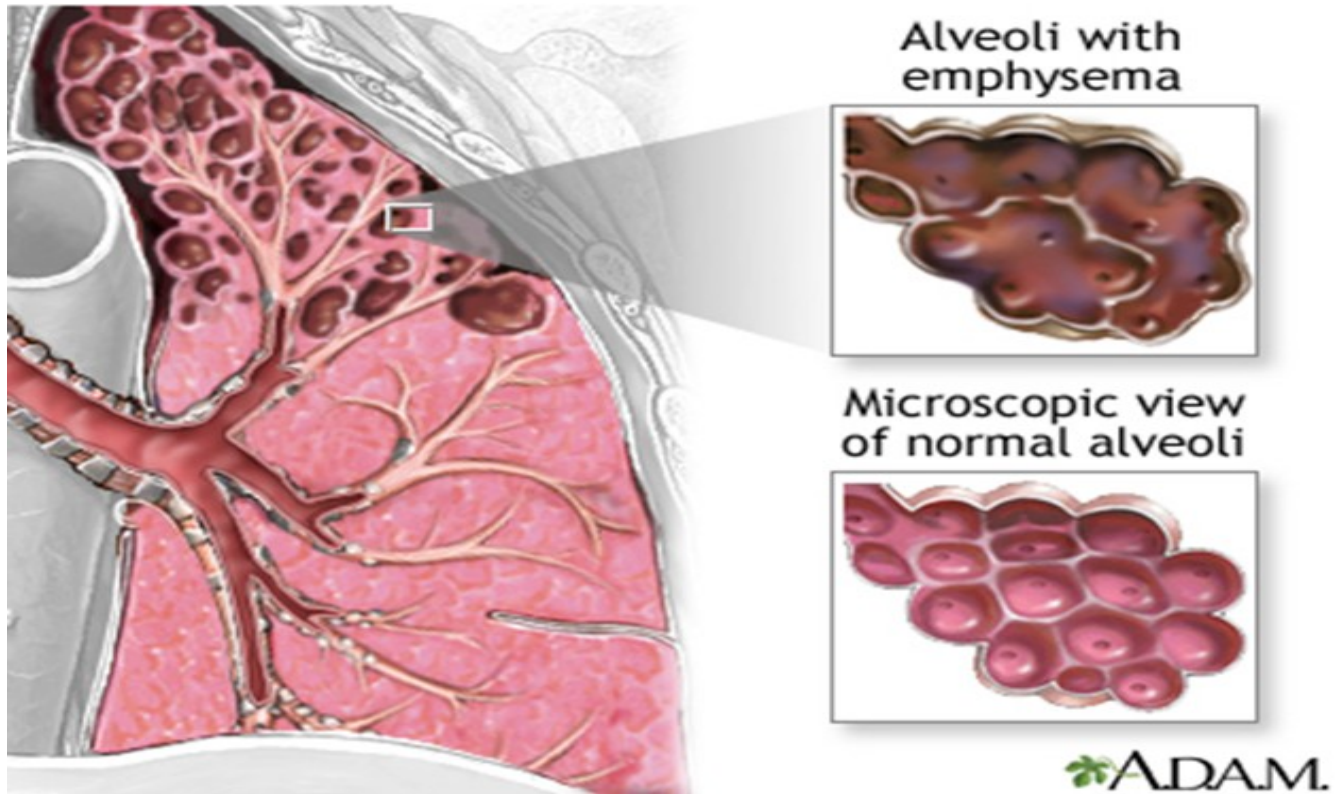
- ✓ Chronic cough
- ✓ Fatigue
- ✓ Dyspnea
- ✓ Production of mucus
- ✓ Shortness of breath
- ✓ Chest discomfort



Chronic bronchitis –
inflammation, excess mucus

Emphysema – alveolar
membrane degradation

Diagnosis of Emphysema

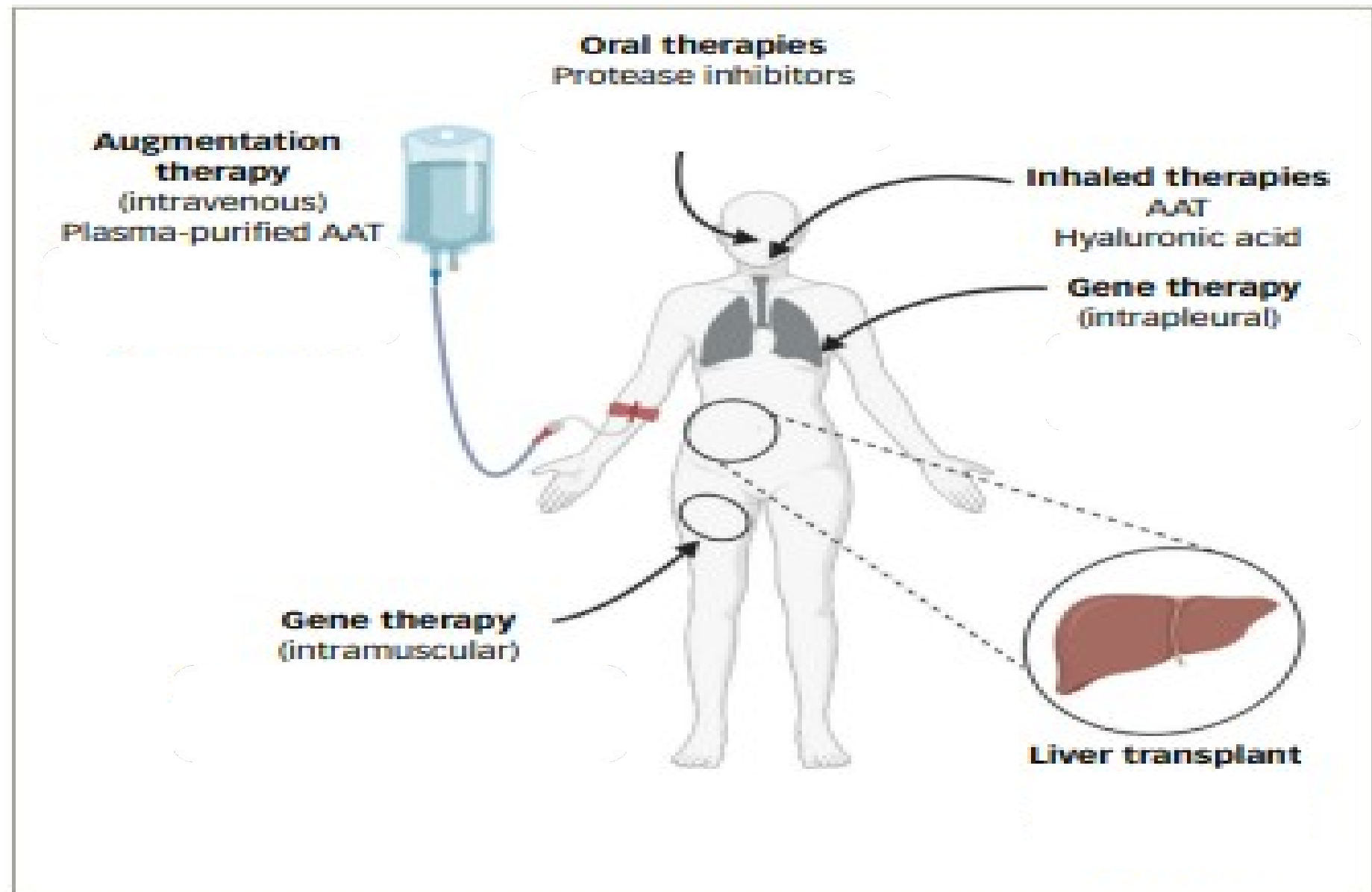


- **Alpha-1 Antitrypsin Test**
- **Lung Function Tests**

Treatment of $\alpha 1$ antitrypsin deficiency

1. Can be treated by IV administration of $\alpha 1$ antitrypsin
2. Gene therapy
3. Treat lung symptoms to improve breathing by:
Bronchodilators & steroids
4. Liver transplant
5. Avoid :
Smoking which aggravate lung disease
Alcohol which worsen liver damage

Figure 1: Schematic of established and novel therapies available for alpha-1 lung disease



Answer the following question

α 1 antitrypsin is mainly synthesized in which of the following organs?

A. Kidneys

B. Liver

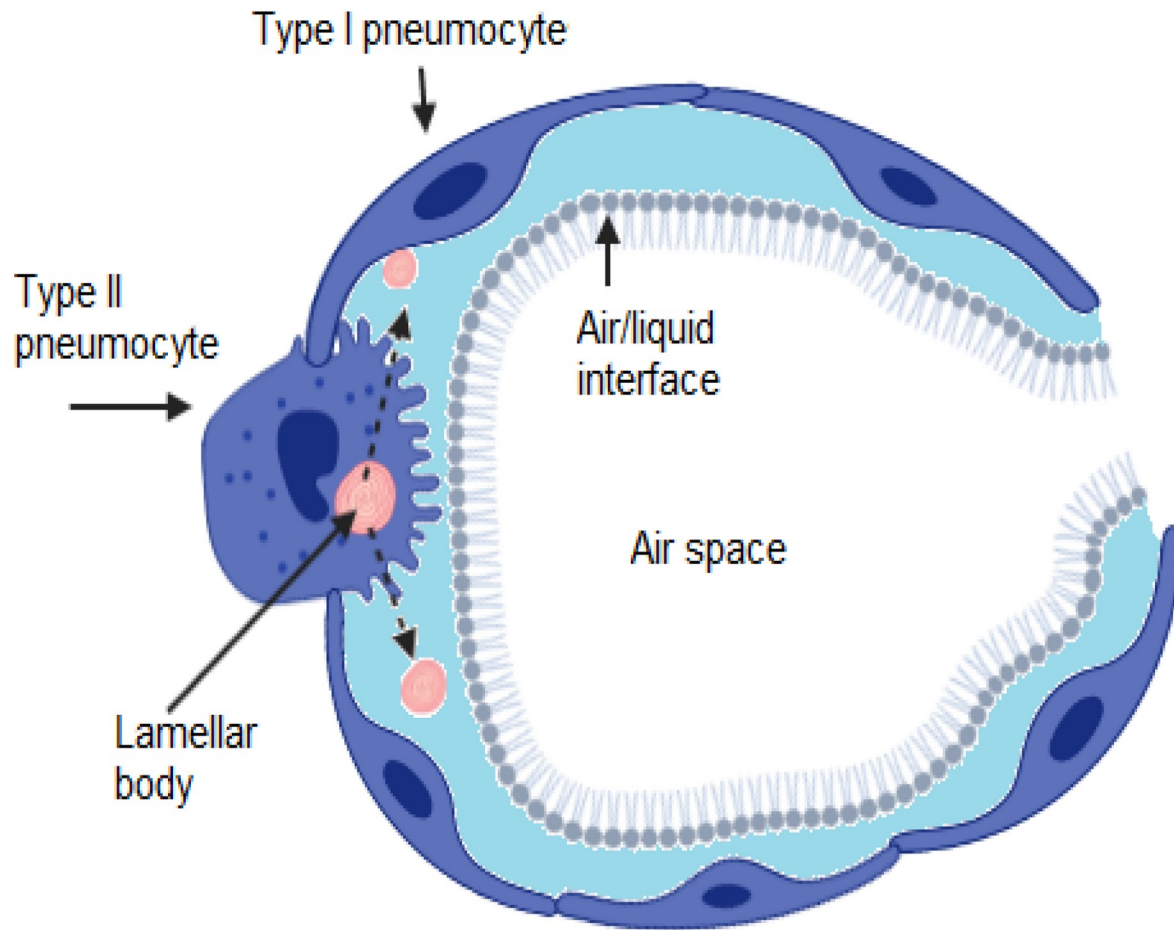
C. Intestines

D. Brain

Gas exchange in the lung takes place in the alveoli.

Oxygen diffuses from the alveoli to the capillaries,

and carbon dioxide leaves the capillaries and



- ❖ **The surface tension of the inner surface originates from the attraction between the molecules of the alveolar fluid.**
- ❖ **Surfactant lowers the surface tension at the alveolar air-fluid interface so prevent lung collapse.**

Composition of lung surfactant

Dipalmitoyl Phosphatidyl choline

1-

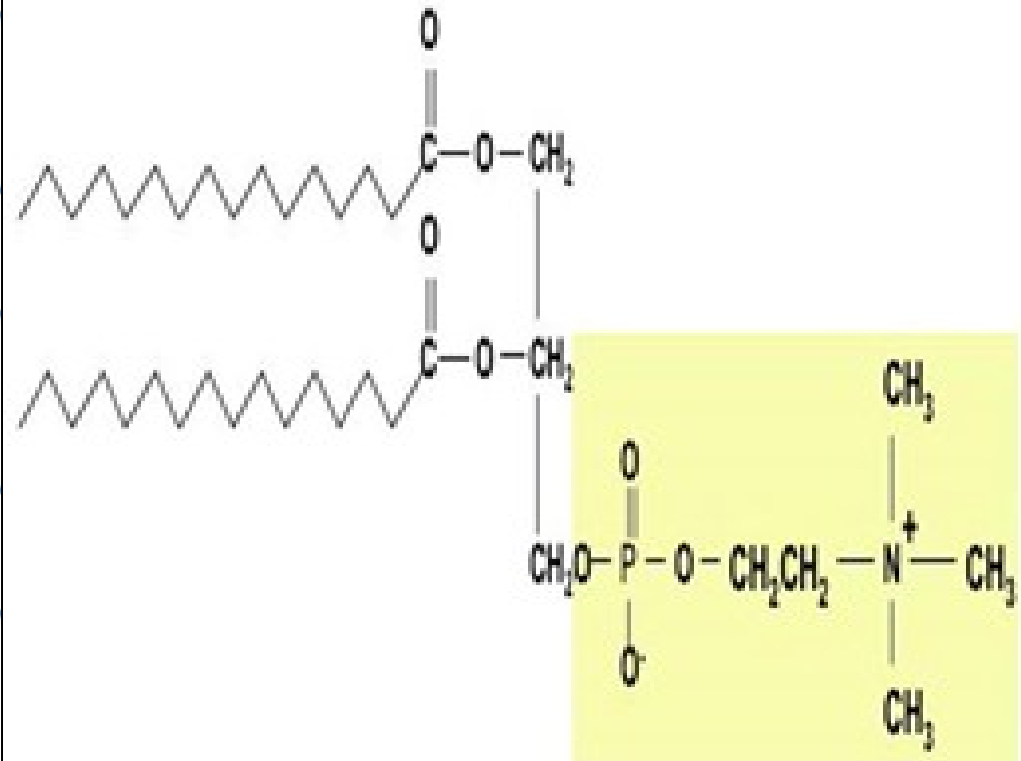
- Glycerol

2-

- Palmitic acid at C1&2

3-

- Phosphoric acid and choline.



In premature babies, the lungs are developmentally deficient in lung surfactant

Key points

- **Cystic fibrosis is caused by mutations in the gene encoding the CFTR protein, a Cl⁻ transporter.**
- **Cystic fibrosis is characterized by the buildup of thick, sticky mucus that can damage many of the body's organs. The most common signs and symptoms include progressive damage to the respiratory system and chronic digestive system problems.**
- **Alpha-1 antitrypsin deficiency is a genetic disorder that may result in lung disease or liver disease. Affected individuals often develop emphysema. Smoking or exposure to tobacco smoke accelerates the appearance of emphysema symptoms and damage to the lungs.**
- **Respiratory distress syndrome (RDS) is a common breathing disorder that affects newborns.**
- **RDS occurs most often in babies born preterm due to lack of surfactant in the lungs.**

References

- **Fundamentals of Clinical Chemistry (Tietz) Sixth**
- **"Textbook of Biochemistry with Clinical Correlations" by T.M. Devlin**
- **"Lippincott's Illustrated Reviews in Biochemistry" by P.C. Champe, R.A. Harvey and D.R. Ferrier**
- **"Harper's Biochemistry" by R.K. Murray, D.K. Granner, P.A. Mayes and V.W. Rodwell.**



Thank
you